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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,519	06/15/2006	Jean-Francois Bonfanti	TIP-0052SPCT	7522

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EXAMINER	
CHANDRAKUMAR, NIZAL S	
ART UNIT	**PAPER NUMBER**
1625	
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09/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,519	BONFANTI ET AL.	
	Examiner	Art Unit	
	Nizal S. Chandrakumar	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/01/2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application filed 06/15/2006 is a 371 of PCT/EP04/53606 12/20/2004 which claims benefit of 60/566,835 04/30/2004.

Applicant's response filed 08/01/2007 is acknowledged.

Applicants cancelled claims 1-21. Added new claims 22-32.

Response to applicants Remarks:

Applicant's amendment to claims overcomes the rejections under *35 USC § 102 set forth in* the previous office action.

Applicant's amendments to claims overcome part of the rejections under *35 USC § 112 (scope of* enablement). The applicant states that 'the Examiner's comments about scope and enablement, together with the indication of allowable subject matter have resulted in the claims scope presented in claims 22-25'.

In the previous office action, with regards to the presence of working example in the specification, the Examiner noted, on page 4 'working examples for preparing, compounds of the formula (I) are limited to **one single** variant of G (methylene), **one single variant of R1** (pyridyl), **one variant for t (2)** and **one variant for R5**.' (emphasis added). As to the limitations of the guidance present in the specification with regards to R1, the Examiner noted, on page 5, "The protocol disclosed for the reaction of 2-chlormethylpyridine derivative would not work with 2-(5-chloropentyl)pyridine, because the leaving group in this case is not activated as in the case of benzylic-type 2-chloromethylpyridine.".

Similar arguments as to the lack of guidance and working example in the specification commensurate with the scope of the claims were presented in the previous office action. Applicant's amendment to limit G to CH2, and R1 to pyridyl addresses only part of the scope of the enablement issues presented earlier.

In the previous office action some of the claims were indicated to be allowable if rewritten to overcome the rejections set for the office action. The amendment to the claims overcome only part of the *35 USC § 112* rejections (scope of enablement). The indicated allowability is withdrawn.

The new claims 22-32 are rejected for the following reasons.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26 (and dependent claims 31 and 32) are rejected under 35 U.S.C. 112, second paragraph, because claim 26 recites the limitation R3b is hydrogen. There is insufficient antecedent basis for this limitation in the claim 26, because claim 26 depends on claim 24 which is drawn to compounds wherein R3b is C1-6alkyl.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New claims 22-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a few variables of the formula (I), does not reasonably provide enablement for the general class of compounds claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims. *As stated in the earlier office action, the working examples described in the specification is enabling for one single variant of pyridine and R5 being H.* The limitations of the new claims partly overcome the enablement rejections set forth in the early office action. The claims still contain subject matter that is not described in the specification in such a way as to enable one skilled in the art to make and use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: breadth of the claims; nature of the invention; state of the prior art; amount of direction provided by the inventor; the level of predictability in the art; the existence of working examples; quantity of experimentation needed to make or use the invention based on the content of the disclosure; and relative skill in the art. All of the factors have been considered with regard to the claim, and the most relevant factors *pertaining to the variables R1 and R5* are discussed below:

The breadth of the claims: The variables R1 and R5 in the formula I are defined as follows:

R^1 is pyridyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of halo, hydroxy, amino, cyano, carboxyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, Ar^1, Ar^1C_{1-6}alkyl, Ar^1C_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)amino-C_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{4a}-, Ar^1-SO_2-NR^{4a}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{4a}R^{4b}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)-, Ar^1C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)-;

R^{4a} and R^{4b} can be the same or can be different relative to one another, and are each independently hydrogen or C_{1-6}alkyl; or

R^{4a} and R^{4b} taken together may form a bivalent radical of formula -$(CH_2)_5$-;

R^5 is hydrogen or C_{1-6}alkyl;

With independently varying multiple variables layered with substituents on top of substituents, not to mention the stereo chemical possibilities resulting from substitutions on tetrahedral carbon substitutions, as well as the variable Q (mentioned in the previous office action), the number of theoretically conceivable compounds for the formula I is in billions, rendering the scope of the claims large, one that is not supported by the disclosure in the specification.

The nature of the invention: The nature of the invention is a large Markush of compounds that are alleged to have the ability to inhibit virus replication.

The existence and absence of working examples: The working examples in the specification for preparing compounds of the formula (I) is limited to compounds with one single variant of pyridyl R1, and one variant for R5, i.e., H. The source for procuring the starting materials (commercial or literature citation) is not disclosed in the specification. There is one example of R1 pyridyl, while R1 is defined to encompass billions of possibilities (see above).

R5 is defined as hydrogen or C1-6 alkyl, while the disclosure is limited to R5 = H.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the art of organic synthesis, it is noted that each embodiment of the invention is required to be individually assessed for viability.

The amount of direction or guidance present: Apart from the generic guidance with hypothetical synthetic schemes on pages 18 and 19, the direction provided in the specification for making the compounds of the formula I is limited with respect to introducing the R1 pyridyl group. The specific working example on page 30 uses a highly reactive chloromethyl substituted pyridine compound for the alkylation of the benzimidazole nitrogen. The success of this reaction is largely due to the high susceptibility of the chloro group for displacement reactions because of the benzylic nature of the substitution and the additional activation provided by the hydroxyl group at the 3-position of the pyridine ring. For this reason, it is the position of the Examiner, that the applicant had possession of only limited number of analogs for the pyridyl R1 group.

In addition, the reaction on pages 29 and 30 of the specification provides reasons on the lack of examples in the specification for compounds wherein R5 is other than hydrogen. The nitrogen of N-R5 is unreactive to a highly activated alkyl halide, providing for the alkylation on the nitrogen of the benzimidazole. For this reason, it is the position of the Examiner, that the applicant did not have possession of compounds of the formula I wherein R5 is other than hydrogen.

There is a complete lack of direction or guidance for procuring the crucial starting materials, i.e., the substituted pyridyl compounds for the displacement reaction shown on page 30. This is of crucial

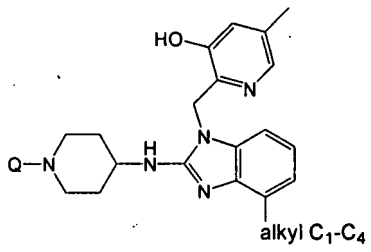
importance, given that the major portion of the core structure of rest of the formula I is known in the prior art (cited by the applicant, Journal of Medicinal Chemistry, 1985, 28(12) 1934-1943). No reference to commercial source or literature citations of procedures for obtaining the starting materials is found in the specification.

The quantity of experimentation needed to make or use the invention: The quantity of experimentation needed is undue. One skilled in the art would be faced with burdensome research in developing strategies with regards to starting materials, reagents or process conditions needed for making the claimed inventions. The protocol disclosed for the reaction of a highly reactive 2-chlormethylpyridine derivative would not work with the numerous possibilities claimed for the pyridyl substitutions. Based on the specification, as discussed above, the introduction of R5 C1-C6 alkyl would require undue research burden because of the highly deactivated nature of the nitrogen attached to the 2-position of benzimidazole. For instance, any strategy to introduce the R5 alkyl group needs undue experimentation to prevent concurrent alkylation of other nitrogens present in the variable Q as well as the nitrogen attached to the variable Q.

With respect to potential biological use of these compounds, the variable R1 pyridyl is defined to be capable of accommodating a variety of groups such as, neutral, basic and acidic groups, groups of varying molecular volumes, lipophilicity, as well as substitutions such as halo-substituted alkyl groups. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity. For these reasons, one of ordinary skill in the art would have to engage in undue experimentation to identify a compound among the plethora of possible structures encompassed by the formula I, that would have the desired RSV inhibiting property, with no assurance of success.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

It is not seen where the specification provides for enablement for compounds other than the following:



Conclusion

Claims 22-32 are rejected. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nizal S. Chandrakumar whose telephone number is 571-272-6202. The examiner can normally be reached on 8.30 am – 5 pm Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at 571-272-0867 or Primary Examiner D. Margaret Seaman can be reached at 571-272-0694. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nizal S. Chandrakumar

D. MARGARET SEAMAN
PRIMARY EXAMINER